

Not typical angina and mortality in women with obstructive coronary artery disease: Results from the Women's Ischemic Syndrome Evaluation study (WISE)

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ABSTRACT

Background: Women frequently present with symptoms not typical of angina (NTA) making ischemic heart disease recognition, diagnosis and treatment challenging. We compared mortality in women with obstructive coronary artery disease (CAD) with NTA vs typical angina (TA).

Methods: We studied 326 Women's Ischemia Syndrome Evaluation (WISE) participants undergoing coronary angiography for suspected myocardial ischemia with core-lab measured obstructive CAD. TA was defined as sub-sternal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin; NTA did not meet criteria for TA. The women were followed for non-fatal events and death for a median of 5.9 and 9.6 years respectively. Multivariate cox proportional hazards regression determined relations to events.

Results: Overall, 115 (35%) of the women had TA. Baseline demographics, risk factors or additional symptom characteristics were similar between the two angina groups. Non-fatal events did not differ between groups. Women with NTA had a higher mortality compared to TA women (36% vs 26%, respectively, $p = 0.047$). Despite adjustment for additional major risk variables, NTA was an independent predictor of mortality compared to TA with a hazard ratio of 1.73 (95% Confidence interval: 1.04, 2.89).

Conclusions: Among women with suspected ischemia undergoing coronary angiography with obstructive CAD, NTA was more common than TA, and predicted a higher longer-term mortality. Further investigation is needed to confirm these results, and investigate potential explanations for the higher mortality observed in women with NTA women, including lower recognition or action in the setting of obstructive CAD.

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1. Background

Women with signs and symptoms of ischemia frequently have symptoms of non-typical angina (NTA) [1–4]. Typical angina (TA), defined as substernal discomfort occurring with physical exertion or emotional stress, and relieved within 10 min by rest or nitroglycerin is frequently used to help predict the presence of

obstructive coronary artery disease (CAD) [2,5]. Although women have a similar incidence of stable angina compared to men [6], studies have shown that typical angina is less likely to be associated with obstructive CAD in women than in men [3,7–10]. Pepine et al. [4] characterized over 5000 outpatients with ischemic heart disease and chronic stable angina and found women were more likely to have atypical features of rest and mental stress angina. Further, women with ischemic heart disease are more likely than men to experience atypical symptoms in locations other than substernal including jaw, arms, shoulder, back, epigastrium as well as associated dyspnea, palpitations, fatigue and nausea [8,11–13].

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While prior work has suggested that angina symptoms are less diagnostic for obstructive CAD in women [3,7–10,14], the predictive value of NTA for mortality in women with obstructive CAD is unknown. Previous studies have shown “nonspecific” chest pain is associated with nearly equal mortality compared to typical angina in men [15], and diabetic stable CAD not stratified by sex had similar mortality rates in asymptomatic, angina equivalents or typical angina [16]. Multiple studies however have found relatively less treatment in women presenting with unstable angina or myocardial infarctions [17–19], and relatively higher mortality [19–23]. We hypothesized that symptoms non typical for angina may contribute to women receiving less recognition, less appropriate treatment and increased mortality. We chose to analyze those with obstructive CAD due to existing guidelines for diagnosis and therapy in this group. As part of the Women’s Ischemia Syndrome Evaluation (WISE) we compared all-cause mortality in women with obstructive CAD with NTA versus TA.

2. Methods

2.1. Study population

The study population included 326 participants with obstructive CAD in the WISE (enrolled 1996–2001), a National Heart, Lung, and Blood Institute-Sponsored four center study [12]. In brief, participants were women over the age of 18 with signs and symptoms of ischemia who were undergoing clinically ordered coronary angiography for suspected myocardial ischemia. Major exclusion criteria include pregnancy, contraindications to provocative diagnostic testing, cardiomyopathy, New York Heart Association class IV congestive heart failure, recent myocardial infarction, significant valvular disease or congenital heart disease, as previously described [12]. In the original WISE cohort of 936 women, 364 (39%) had obstructive CAD. The current sample of 326 women includes all WISE women with obstructive CAD who could be classified as having either symptoms of typical (TA) or not typical of angina (NTA) and who had follow-up information. The study protocols were each approved by the site institutional review boards. Informed consent was obtained and all women were followed for at least one year to assess clinical events and symptom status.

2.2. Baseline testing

All participants underwent an initial evaluation that included demographic, medical history, physical exam, psychosocial and symptom questionnaires. Blood samples including fasting blood glucose, lipids, creatinine, hemoglobin and high sensitivity C reactive protein were collected at baseline. Psychosocial questionnaires included Beck Depression and Spielberg anxiety. The complete study design and cited methodology of the WISE study have been described [12].

2.3. Angiographic assessment of obstructive CAD

As part of the WISE entry criteria, all women underwent clinically ordered angiography conducted for suspected myocardial ischemia. Coronary angiograms were analyzed by a WISE angiographic core laboratory (Rhode Island Hospital, Providence, RI, USA), masked to clinical data, as previously described [20]. The presence of obstructive CAD was defined $\geq 50\%$ stenosis ≥ 1 major epicardial coronary artery. An angiographic CAD severity score was calculated based on stenosis severity as previously published [20].

2.4. Definition of symptoms of not typical of angina versus typical angina assessment

Symptoms were assessed at baseline. Traditional chest pain assessment, validated in large female and male populations for obstructive CAD predictions was used to classify symptoms as TA [5]. TA was defined as meeting all 3 criteria: (1) substernal discomfort, (2) precipitated by physical exertion or emotional stress, and (3) relieved within 10 min by rest or nitroglycerin and has been used to help predict the presence of obstructive coronary artery disease (CAD) [5]. NTA was defined as all other angina symptoms not meeting criteria for TA. Additionally, a subgroup of 222 women was administered a comprehensive symptom check list developed by WISE investigators after baseline testing had already been completed, to better characterize and understand symptoms not typical for angina.

2.5. Patient follow-up

During the initial follow-up phase, taking place over a median of 5.9 years (interquartile range, 2.8, 7.0), participants were contacted at 6 weeks after baseline testing and then annually. Each woman was queried about symptoms, medication use, cardiovascular events, hospitalizations or revascularization procedures since last contact. In the event of a death, a death certificate was obtained as well as descriptions by an attending physician and/or primary relative regarding the circumstances of the death. A National Death Index (NDI) search was subsequently conducted and death certificates obtained which extended the follow-up for mortality to a median of 9.6 (interquartile range 8.5, 10.5), up to a maximum of 11.5 years. A major adverse cardiac event was defined as death, non-fatal myocardial infarction, non-fatal stroke, or heart failure hospitalization. All-cause death was used, as the ultimate outcome increasingly used in studies and clinical trials, and due to the concern that death may be less commonly adjudicated as cardiovascular in women with atypical symptoms.

2.6. Statistical methods

Baseline demographics and symptom categories were compared between NTA and TA using t-tests for continuous variables and Chi-squared tests for categorical variables. Time to death among patients with TA and NTA was analyzed and plotted using Kaplan-Meier analyses. The association between survival and NTA and TA were adjusted for age and medical history indicators of hypertension, dyslipidemia, diabetes, tobacco use, and family history of CAD using a Cox Proportional Hazards regression, and reported with a hazard ratio and 95% confidence interval. A significance level of 0.05 was used for all hypothesis tests. All analyses were done using SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

In this subsample of 326 WISE participants with angiographically confirmed obstructive CAD, only 115 (35%) had TA while the remainder 211 (64%) had symptoms defined as NTA. The baseline characteristics depicted in Table 1 demonstrate similar demographic, risk factor, and psychosocial profiles in the NTA and TA groups. The only exception was that women with NTA were more likely to be using ACE inhibitors ($p = 0.033$), a finding that is expected to occur by chance given the number of items assessed. Medication used at baseline and follow up did not differ other than the ACE inhibitor. Detailed symptom characterization demonstrated higher rates of left sided chest pain ($p = 0.022$) in NTA women and higher rates of chest pressure in TA women

Table 1
Baseline characteristics for NTA vs. TA.

	NTA n = 211	TA n = 115	p- value
Age, years	61.8 ± 11.4	61.7 ± 11.7	0.96
Obese (BMI ≥ 30)	77 (37%)	45 (39%)	0.76
White/Non-Hispanic	160 (76%)	93 (81%)	0.30
Post-Menopausal	171 (83%)	97 (85%)	0.63
Current Smoker	49 (23%)	23 (20%)	0.50
Ever Smoked	126 (60%)	64 (56%)	0.48
Diabetes	85 (41%)	39 (34%)	0.23
History of Dyslipidemia	131 (68%)	75 (70%)	0.65
History of Hypertension	147 (70%)	69 (60%)	0.07
Family History of CAD	142 (70%)	72 (65%)	0.39
Coronary Severity Score	27 ± 17	26 ± 16	0.54
Beck Depression	11.8 ± 8.6	10.8 ± 8.7	0.47
Spielberger Anxiety	19.4 ± 5.6	19.0 ± 5.7	0.70
DASI	16.6 ± 12.6	15.1 ± 11.9	0.30
Symptom intensity (usual)*	2.6 ± 1.1	2.5 ± 1.0	0.24
Symptom intensity (at worst)*	4.0 ± 1.2	4.0 ± 1.0	>0.99
Symptoms almost ≥ every day	81 (38%)	54 (47%)	0.13
Perceived Quality of Life	6.9 ± 2.4	7.0 ± 2.0	0.56
History of HRT	92 (45%)	54 (47%)	0.70
Baseline Lab Results			
Total Cholesterol (mg/dL)	196 ± 44	196 ± 52	0.97
Triglycerides (mg/dL)	178 ± 141	170 ± 107	0.62
High density lipoprotein (mg/dL)	53 ± 13	52 ± 10	0.84
Low density lipoprotein (mg/dL)	112 ± 39	110 ± 45	0.83
Glucose (fasting) (mg/dL)	135 ± 70	129 ± 78	0.48
Creatinine (mg/dL)	0.95 ± 0.60	0.90 ± 0.67	0.54
Hemoglobin (g/dL)	12.8 ± 1.4	13.0 ± 1.4	0.40
High sensitivity-C reactive protein (mg/L)	0.98 ± 1.77	1.38 ± 2.49	0.20
Medications at Baseline			
ACE Inhibitors	77 (37%)	29 (25%)	0.033
Angiotensin Receptor Blockers	8 (4%)	6 (5%)	0.56
Diuretic	71 (34%)	39 (34%)	0.99
Calcium Channel Blockers	70 (34%)	35 (30%)	0.62
Aspirin	158 (75%)	89 (77%)	0.66
Beta Blockers	109 (52%)	52 (45%)	0.23
Statins	76 (36%)	33 (29%)	0.16
Nitrates	108 (52%)	63 (55%)	0.59

HRT = hormone replacement therapy, ACE = angiotensin converting enzyme inhibitor, BMI = body mass index, CAD = coronary artery disease, DASI = Duke Activity Status Inventory.

* Symptom intensity, range 1 (lowest) – 5 (highest).

($p = 0.043$) (Table 2), but was otherwise not informative beyond the traditional angina classification.

Over a median of 5.9 years, 18 women (5.5%) experienced a non-fatal myocardial infarction, 22 (6.7%) a non-fatal stroke, 35 (11%) were hospitalized for heart failure, and 126 experienced at least one hospitalization for recurrent chest pain. NTA women had similar rates of major cardiac events compared to TA women, although there was a trend toward double the rate of heart failure hospitalizations (Table 3).

Over a median of 9.6 years, 107 (33%) women died. Those with NTA had a higher mortality rate (36% vs 26%, respectively, age-adjusted log-rank $p = 0.047$) (Table 3), with a hazard ratio (95% confidence interval) of 1.55 (1.005, 2.40). NTA remained a strong predictor after adjusting, in addition, for baseline tobacco use, history of diabetes, hypertension, dyslipidemia and family history of CAD (HR 1.73, 95% CI 1.04, 2.89) (Fig. 1).

4. Discussion

Our results demonstrate in women with suspected ischemia undergoing coronary angiography with obstructive CAD, that NTA is more common than TA, however further angina characterization did not appear to be informative. Notably, we observed a higher all-cause mortality in the NTA vs TA group at 10-year

Table 2
Subgroup Symptom Analysis for NTA vs. TA, n = 222.

Symptom	NTA (n = 143)	TA (n = 79)	p
Left side of chest	52 (36%)	17 (22%)	0.022
Neck or jaw	32 (22%)	22 (28%)	0.36
Left arm	51 (36%)	25 (32%)	0.54
Abdominal pain	18 (13%)	10 (15%)	0.62
Arm/shoulder pain	91 (64%)	50 (76%)	0.11
Back Pain	66 (47%)	22 (33%)	0.056
Chest Pain	104 (74%)	53 (80%)	0.34
Chest Pressure	97 (69%)	55 (82%)	0.043
Chest tightness	88 (63%)	48 (73%)	0.18
Chest heaviness, burning, tenderness	96 (67%)	51 (76%)	0.70
Cough	33 (24%)	18 (27%)	0.56
Dizziness, lightheadedness	70 (50%)	29 (43%)	0.34
Feel lousy	71 (51%)	41 (62%)	0.12
Heartburn/indigestion/stomach problem	61 (43%)	27 (40%)	0.60
Impending doom	25 (18%)	11 (17%)	0.69
Jaw pain	38 (27%)	14 (21%)	0.46
Fainting	9 (6%)	7 (11%)	0.29
Nausea/vomiting	38 (27%)	18 (27%)	0.98
Neck pain	48 (34%)	19 (29%)	0.43
Numbness/tingling in arm or hand	67 (48%)	35 (53%)	0.49
Palpitations	61 (44%)	32 (49%)	0.54
Shortness of breath	97 (69%)	47 (72%)	0.61
Sweating	63 (45%)	28 (42%)	0.69
Weakness, fatigue, faintness	74 (52%)	39 (58%)	0.44
Pain wakes patient at night	65 (48%)	30 (45%)	0.68

Bold values denotes Higher rates of chest pressure in women with TA.

follow-up – these findings are relevant because all women underwent clinically indicated coronary angiography and access to diagnostic resources cannot be blamed. There were similar rates of major adverse cardiac events, with a trend toward increased heart failure hospitalization in NTA women. Adjustment for baseline differences, including a relatively higher ACE use among NTA, did not substantially alter the results and further suggest that access to therapeutic resources also did not contribute to the adverse outcome.

Women with NTA were more often on an ACE inhibitor suggesting they were more hypertensive, and although adjustment for these important risk variables did not alter the mortality results, there may be pathophysiological links between hypertension and symptom quality. Increased myocardial oxygen demand and diminished coronary blood flow and/or coronary flow reserve is related to hypertension [24], leading to left ventricular impedance and intramyocardial wall tension, increasing myocardial demand leading to angina [24]. Another possible link is the damage to the endothelial function caused by persistent hypertension which may cause a different constellation of symptoms and or increase risk of CV events [24]. In a study comparing presentation, treatment and outcomes of MI in men versus women, women were more often hypertensive [22]. Perhaps those with NTA and hypertension will help identify those at a higher risk for CV outcomes; further work is needed to help understand this elevated risk.

Our results are consistent with prior work demonstrating that women more often present with atypical symptoms [1,4,5,8], and our hypothesis that symptoms non typical for angina may contribute to women receiving less recognition, less appropriate treatment and increased mortality. Our results demonstrating elevated mortality in women with NTA compared to TA suggests the possible explanation that atypical symptoms may contribute to the observed lower use of lifesaving treatments and have worse outcomes in women with CAD [18,19,21,22,25]. We focused on all-cause mortality due to concerns for underdiagnosis of CVD related deaths in women who present with atypical symptoms. Prior WISE work has demonstrated a majority of the deaths in this population are adjudicated to be cardiovascular deaths [26,27]. Women with

Table 3
All-cause Mortality and Major Adverse Cardiac Events in NTA vs TA.

	NTA n = 211	TA n = 115	p-value (Age Adjusted)	p-value (Full Model Adjusted)
9.6 Year (Median) Events				
All-cause Mortality	77 (36%)	30 (26%)	0.047	0.035
6.0 Year (Median) Events				
Non-fatal Myocardial Infarction	13 (6%)	5 (5%)	0.42	0.18
Non-fatal Stroke	15 (7%)	7 (6%)	0.68	0.79
Heart Failure Hospitalization	27 (13%)	8 (7%)	0.09	0.31
Angina Hospitalization	81 (39%)	45 (41%)	0.97	0.72
Any Major Event*	90 (43%)	43 (38%)	0.29	0.33

* Major events include death (up to 8 years) and non-fatal myocardial infarction, stroke, or heart failure hospitalization.

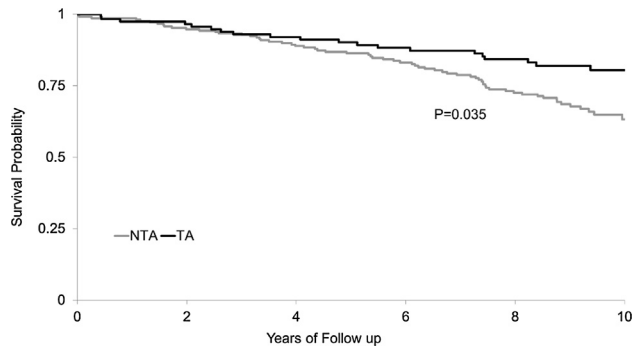


Fig. 1. Fully adjusted Kaplan-Meier plot for 10-year All-Cause Mortality in Not-Typical Angina (NTA) (n = 211) vs Typical Angina (TA) (n = 115).

NTA had at least similar rates of major adverse cardiac events compared to TA. Therefore, women with NTA and suspected or proven obstructed CAD need careful attention and perhaps greater monitoring due to their atypical symptoms. Of note, sex-specific presentation, pathophysiological mechanisms and outcomes remain evident, and cardiovascular disease remains the leading cause of death among women [23].

NTA was more common than TA in patients undergoing clinically indicated coronary angiogram for suspected CAD, even in those who were found to have obstructive CAD [28]. Historically, predicting the likelihood of obstructive CAD has been challenging in women. Once diagnosed with obstructive CAD and stable angina the use of guideline-driven medical therapy is not optimal in women and men [25]. A proposed algorithm from these results of potential relevance to clinical care to close the adverse outcomes preferentially experienced by women would be to consider the presence of symptoms suggestive of ischemia and not the strict definition of TA used in the past when treating women with known obstructive CAD. Further investigation is needed to improve diagnostic and therapeutic strategies in women who present with NTA.

4.1. Limitations

Our study limitations include use of a relatively small, but carefully phenotyped population of women. Further, our use of clinically referred cohort which may not be representative of all women with suspected ischemia and obstructive CAD. Follow-up events were gathered per patient report with confirmation by medical records and cause of death, which could result in reporting bias. Our lack of information about CAD extent and revascularization treatment is a limitation and may have influenced prognosis. Our use of all-cause mortality could be misleading, however this is considered a strength as the ultimate outcome in studies and trials, and prior WISE work has demonstrated a majority of the deaths in this population are adjudicated to be cardiovascular

deaths [26,27]. Another important limitation includes having a low statistical power for the non-fatal events which we only followed for 6 years.

5. Conclusions

Among women with suspected ischemia undergoing coronary angiography with obstructive CAD, NTA was more common than TA, and predicted a higher longer-term mortality. Further investigation is needed to confirm these results and investigate potential explanations for the higher mortality observed in women with NTA women, including lower recognition or action in the setting of obstructive CAD.

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